102. (New) The method of Claim 85 wherein said mammalian CXCR3 protein or ligand binding variant comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2).

103. (New) The method of Claim 87 wherein said mammalian CXCR3 protein or ligand binding variant comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2).

104. (New) The method of Claim 89 wherein said mammalian CXCR3 protein or functional variant comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2).

105. (New) The method of Claim 91 wherein said mammalian CXCR3 protein or functional variant comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2).

REMARKS

Claims 30, 34, 37, 38, 40-42, 44, 46, 48, 60-75, 81 and 85-92 been amended and Claims 93-105 are new. Claims 30-52 and 60-105 are pending.

The title and abstract have been amended to reflect the subject matter of the pending claims.

Claims 30, 34, 38, 42, 46 and 48 have been amended to recite that the CXCR3 protein or variant shares at least about 80% amino acid sequence identity with SEQ ID NO:2.

Claims 60, 63 and 66 have been amended to recite "mammalian CXCR3 protein or variant shares at least about 90% amino acid sequence identity with SEQ ID NO:2."

Claims 61, 64 and 67 have been amended to recite that the CXCR3 protein or variant "is encoded by a nucleic acid sharing at least about 75% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1."

Claims 62, 65 and 68 have been amended to recite " mammalian CXCR3 protein or variant is encoded by a nucleic acid sharing at least about 90% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1."

Claim 75 has been amended to recite "and comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2)."

Claim 81 has been amended to recite "human CXCR3 protein," and "comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2)."

Claim 85 has been amended to recite that the mammalian CXCR3 protein or ligand binding variant is encoded by a nucleic acid that hybridizes, under the recited wash conditions to "a nucleic acid selected from the group consisting of:

a) the complement SEQ ID NO:1; and

b) the complement of a portion of SEQ ID NO:1 comprising the open reading frame."

Claims 87, 89 and 91 have been amended to recite that the mammalian CXCR3 protein or ligand binding variant is encoded by a nucleic acid that hybridizes, under the recited wash conditions to "a nucleic acid selected from the group consisting of:

i) the complement SEQ ID NO:1; and

ii) the complement of a portion of SEQ ID NO:1 comprising the open reading frame."

Support for the amended claims is found throughout the application as filed, for example, at page 17, lines 3-13; page 19, lines 17-25; page 19, line 35 through page 20, line 8; and page 18, line 32 through page 19, line 16.

Support for new Claims 93-105 is found, for example, at page 17, lines 6-12.

The amended claims and new claims are supported by the application as filed. Therefore, this Amendment adds no new matter.

Additional remarks are set for below with reference to the rejections set forth in the Office Action.

Objection to the Specification

The title of the application is objected to as not being descriptive.

The title and abstract have been amended to reflect the claimed subject matter, thereby obviating the objection.

Rejection of Claims 75-79, 81, 82 and 84 Under the Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 75-79, 81, 82 and 84 are rejected under the judicially created doctrine of obviousness-type double patenting over Claims 31-34 of U.S. Patent No. 6,140,064.

Applicants will consider filing a terminal disclaimer if claims deemed to be conflicting with Claims 31-34 of U.S. Patent No. 6,140,064 are indicated as being allowable.

Rejection of Claims 30-52, 60-74 and 85-92 Under 35 U.S.C. § 112, First Paragraph

Claims 30-52, 60-74 and 85-92 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that the specification contains adequate written description of methods of detecting or identifying an agent with binds a human CXCR3 with an amino acid sequence as set forth in SEQ ID NO:2, by fails to adequately describe a method of detecting or identifying an agent which binds a mammalian CXCR3. The Examiner further states "[t]he skilled artisan cannot envision all the possible mammalian CXCR3 proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used." Office Action, at page 5, lines 15-17. The Examiner goes on to state that the claims are genus claims, and that the specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. In the Examiner's estimation, the genus is highly variant, and one of skill in the art would

conclude that the disclosure fails to provide a representative number of species to describe the genus. The Examiner cites Fiers v. Revel, 25 USPQ2d 1601 (Fed. Cir. 1993), Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991) and Fiddes v. Baird, 30 USPQ2d 1481 (Bd. Pat. App. & Inter. 1993) as supporting the rejection.

In Amgen, the court held that conception of a claimed gene requires that the inventor "be able to define it so as to distinguish it from other materials, and to describe how to obtain it." Amgen, 18 USPQ2d at 1021. The court stated that it is not sufficient to define a DNA solely by its principal biological property (i.e., the protein it encodes), but that conception occurs when "one has a mental picture of the structure of the chemical [DNA], or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it." Id. (emphasis added). Thus, Amgen specifically provides that conception of a claimed nucleic acid is not dependent on the inventor's ability to define the nucleic acid by its nucleotide sequence. There is no requirement in law that the skilled man be able to specifically envision all possible species encompassed by the claim or that all encompassed species be reduced to practice.

In Fiers, the court applied the Amgen standard of conception in determining priority of invention in a three party interference. The court also adopted the conception standard of Amgen for evaluating the sufficiency of written description stating, "[i]f a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity." Fiers, 25 USPQ2d at 1603. The Fiers interference involved a single count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

The court held that junior party Fiers was unable to establish a date of conception prior to the filing date of his application and did not address the written description requirement of 35 U.S.C. § 112. Fiers, 25 USPQ2d at 1604, 1605.

Junior party Revel attempted to establish priority based upon the filing date of his Israeli priority application, which disclosed a method for isolating a fragment of the DNA and a method

for isolating a messenger RNA coding for Interferon-beta, but did not disclose a complete DNA sequence coding for interferon-beta. Id. at 1603. In evaluating Revel's priority claim, the court focused on whether the Israeli application contained a written description of the DNA of the count. The court found that the Israeli application did not describe the DNA itself, and noted that the application did not even demonstrate that the disclosed methods would lead to the DNA. The court held that Revel's Israeli application did not satisfy the written description requirement of 35 U.S.C. § 112. Id.

In contrast, senior party Sugano's Japanese priority application disclosed the complete nucleotide sequence of a DNA coding for interferon-beta and a method for isolating that DNA. Id. at 1603. The court concluded that "Sugano's application satisfies the written description requirement since it sets forth the complete and correct nucleotide sequence of a DNA coding for β-IF and thus 'convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, [Sugano] was in possession of the [DNA coding for β-IF].'" Id. at 1607. Accordingly, the court affirmed the award of priority to Sugano. Id.

Fiddes v. Baird is an interference between two applications which claimed recombinant DNA molecules encoding basic fibroblast growth factor. The interfering subject matter was defined by the following count:

> A recombinant DNA molecule consisting essentially of a DNA sequence encoding mammalian basic fibroblast growth factor.

Fiddes, 30 USPQ2d at 1481.

One of the issues the Board ruled on was whether Baird's claims that corresponded to the count were anticipated by certain references under 35 U.S.C. § 102(b). Baird attempted to antedate the references by relying on a priority claim to his earlier filed application (which issued as U.S. Patent 4,956,455, '455) which disclosed the amino acid sequence of bovine pituitary FGF, a theoretical DNA sequence encoding same and a method for isolating a cDNA encoding bovine pituitary FGF. Fiddes, 30 USPQ2d at 1482-83.

The Board evaluated Baird's priority claim by looking to the disclosure of the '455 patent to determine if it contained a written description of the broad class of mammalian FGFs. The

Board followed Fiers, holding that the '455 patent did not contain a written description of Baird's claims that corresponded to the count, because the patent did not demonstrate that Baird was "in possession of the naturally occurring gene encoding bovine pituitary FGF," or "in possession of either the amino acid sequence for any other mammalian FGF or any naturally occurring gene encoding any mammalian FGF other than bovine pituitary FGF." Id. at 1483. Because the application that became the '455 patent did not contain a written description of the broad class of mammalian FGFs, Baird was not entitled to the benefit of that application. Id. at 1484.

University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997) is another case relating to written description of claimed nucleic acids. In Eli Lilly, the court found claims of U.S. Patent No. 4,652,525 (the '525 patent), drawn toward DNA encoding vertebrate, mammalian or human insulin to be invalid for lack of an adequate written description of the claimed subject matter. The disclosure of the '525 patent includes the nucleotide sequence of a cDNA encoding rat insulin and a prophetic example teaching a method for isolating a cDNA encoding human insulin ('525 patent at Examples 5-6). However, the claims did not recite structural or physical/chemical features that were sufficient to distinguish the claimed cDNAs from other materials, and the patent does not include a description of the features of any cDNAs encoding insulin other than rat insulin. The court held that a description of rat insulin cDNA is not a description of the claimed broad class of vertebrate, mammalian or human cDNA, stating:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Id. at 1406. The court recognized that adequate description of a genus of cDNAs can be achieved by distinguishing the members of the genus from other materials in other ways. However, the court did not speculate as to what other ways might be proper. Id.

Applicants' specification contains an adequate written description of the claimed subject matter and is readily distinguished from Fiers, Fiddes and Eli Lilly. In Fiers, Fiddes and Eli Lilly, the court or Board was looking at a generic count (or claims corresponding to a generic count) or at generic claims which defined the claimed DNA solely by its biological function (i.e.,

encoding human fibroblast interferon-beta polypeptide, mammalian basic fibroblast growth factor, or vertebrate, mammalian or human insulin, respectively). In order to satisfy the written description requirement of 35 U.S.C. § 112 in those cases, the specifications needed to describe the DNA of the count itself by its structure, method of preparation, physical or chemical properties or whatever other characteristics distinguish the DNA from other materials.

In Fiers, junior party Revel's priority document did not describe the DNA of the count itself, but merely described methods purported to be suitable for isolating the DNA. In contrast, Sugano's priority application described a DNA of the count by its structure, and thus satisfied the written description requirement of 35 U.S.C. § 112.

In Fiddes, the '455 patent disclosed the amino acid sequence of bovine pituitary FGF and a theoretical DNA sequence encoding the protein. However, the count was drawn to a recombinant DNA molecule encoding mammalian FGF and Baird's claims 23, 24 and 26 were drawn to an isolated or synthetic, substantially pure DNA sequence encoding mammalian FGF. Fiddes, at 1481-82. The '455 patent did not describe any naturally occurring DNA or any naturally occurring gene encoding any mammalian FGF other than the theoretical sequence encoding bovine pituitary FGF by structure, method of preparation, physical or chemical properties or any other characteristics that distinguish the DNA from other materials and, therefore, did not satisfy the written description requirement of U.S.C. § 112. The Board's holding and analysis in Fiddes, is similar to that employed by the Federal Circuit in evaluating written description of generic claims in Eli Lilly.

The claims of the subject application define the CXCR3 protein or variant by reciting a combination of function (e.g., binds IP-10 and/or MIG) and structure (at least about 80% or 90% amino acid sequence identity to SEQ ID NO:2; encoded by a nucleic acid with at least about 75% or 90% nucleotide sequence similarity with the coding region of SEQ ID NO:1) or physical/chemical properties (hybridizes to the complement of SEQ ID NO:1 or the complement of a portion thereof comprising the open reading frame) which distinguish the CXCR3 protein or variant from other materials. Therefore, a determination of whether the specification contains an adequate written description must focus on whether the specification conveys to those skilled in

the art that Applicants were in possession of a CXCR3 protein or variant having the properties recited in the claims when the application was filed.

The subject application, unlike Revel's priority application in Fiers, discloses a human CXCR3 by amino acid sequence and a naturally occurring DNA encoding said human CXCR3 by nucleotide sequence. Therefore, the disclosure of the subject application is similar to, but more extensive than that of Sugano's Japanese priority document, which the Federal Circuit held to satisfy the written description requirement of 35 U.S.C. § 112.

The subject application is also distinguished from the '455 patent in Fiddes which discloses a theoretical DNA by nucleotide sequence, but contains no description of any features of the DNAs encompassed by the claimed broader class of mammalian DNA. In contrast, in addition to disclosing the amino acid sequence of a human CXCR3 protein and the nucleotide sequence of a cDNA of a naturally occurring DNA sequence encoding the CXCR3 protein, Applicants' specification describes the broader class of CXCR3 proteins and variants encompassed by the claims by disclosing a combination of function (e.g., binds IP-10 and/or MIG) and structural features (at least about 80% or 90% amino acid identity to SEQ ID NO:2; encoded by a nucleic acid with at least about 75% or 90% nucleotide sequence similarity with the coding region of SEQ ID NO:1) or physical/chemical properties (hybridizes to the complement of SEQ ID NO:1 or the complement of a portion thereof comprising the open reading frame) which are sufficient to distinguish the CXCR3 protein and variants encompassed by the claims from other materials. Specification at page 17, lines 6-12; page 18, line 32 through page 19, line 25; and page 20 line 23 *et seq.*, for example.

Eli Lilly expressly provides that written description of a genus can be achieved by "a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id. (emphasis added) Thus, following the standard of Fiers, Fiddes and Eli Lilly, Applicants' specification includes a written description of the claimed subject matter that is adequate to convey to the person of skill in the art that Applicants were in possession of the claimed subject matter at the time the application was filed.

The rejection is inconsistent with the Patent Office's understanding of the law and binding precedent as evidenced by Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 FR 1099 ("Guidelines") and associated training materials (available on line at http://www.uspto.gov/web/offices/pac/writtendesc.pdf). It is acknowledged that the Guidelines and training materials do not have the force of law. However, because the rejection is based upon substantive patent law, it is appropriate to look to the Guidelines and training materials, and the analytical framework described and illustrated therein, for guidance in applying the substantive law to the facts of the case.

The written description requirement is satisfied where the specification describes the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Vas-Cath, Inc. v Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). The Guidelines specifically provide that when a genus is claimed, the written description requirement may be satisfied by sufficient description of a representative number of species within the genus. Guidelines, 66 FR at 1106. If the genus encompasses species having substantial variation, a sufficient number of species that reflect the variation within the genus must be described. Id. However, where there is not substantial variation among species encompasses by the genus, description of a single species can adequately support claims to the genus. Id.

The training materials include examples which illustrate the application of substantive law to particular facts.

Example 14

Example 14 on page 53 of the training materials relates to written description of claims drawn to a protein and variants thereof which have a specified catalytic activity. In particular, in Example 14, the specification is said to disclose a single protein, that catalyzes the reaction A → B, by amino acid sequence (SEQ ID NO:3) and contemplates but does not exemplify variants having all or any of the following: substitutions, insertions and deletions. The specification is further said to indicate that procedures for producing such variants are conventional in the art and

to disclose an assay for detecting the catalytic activity of the protein. The application is said to contain the following claim:

> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B.

The claim is drawn to a genus of proteins that are defined by function (catalyze the reaction of A → B) and structural features (SEQ ID NO:3, at least 95% identical to SEQ ID NO:3). The analysis presented in the Guidelines states that the claim has two generic embodiments 1) a protein which comprises SEQ ID NO:3; and 2) variants of SEQ ID NO:3.

Because a genus is claimed, the written description requirement may be satisfied by sufficient description of a representative number of species within the genus. The analysis present in Example 14 of the training materials, focuses on whether the specification satisfies the written description requirement by describing a representative number of species within the genus. "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." Guidelines, 66 FR at 1106.

According to the analysis, SEQ ID NO:3 is novel and nonobvious, and was actually reduced to practice. In addition, the specification and claim are said to reveal that:

1) the genus of proteins that are variants of SEQ ID NO:3 does not have substantial variation because all variants must have at least 95% identity to SEQ ID NO:3 and must have the specified activity; and
2) the single disclosed species (SEQ ID NO:3) is representative of the claimed genus because all members of the genus have at least 95% identity to SEQ ID NO:3 and because an assay suitable for identifying all variants that have the specified activity is disclosed.

Based on these findings, the specification in Example 14 of the training materials is said to meet the written description requirement of 35 U.S.C. § 112 for the claim.

The subject application is similar to Example 14 of the training materials in that the claims recite CXCR3 proteins or variants and define the CXCR3 proteins or variants by function (e.g., binds IP-10 and/or MIG) and structural features (at least about 80% or 90% amino acid sequence identity to SEQ ID NO:2; encoded by a nucleic acid with at least about 75% or 90% sequence similarity with the coding region of SEQ ID NO:1) or physical/chemical properties (hybridizes to the complement of SEQ ID NO:1 or the complement of a portion thereof comprising the open reading frame). However, the subject application contains a more extensive written description of the claimed invention than does the specification in Example 14 of the training materials. For example, the application discloses multiple methods for assessing binding to CXCR3 and describes the broader class of CXCR3 proteins or ligand binding variants used in the claimed methods by describing a combination of function and structural or physical/chemical features which are sufficient to distinguish the members of the genus from other materials.

Applying the analysis from Example 14 of the training materials to the claims of the subject application that recite percent amino acid sequence identity reveals:

1) the genus of CXCR3 proteins or ligand binding variants does not have substantial variation because all CXCR3 proteins or variants must have the specified binding activity and have at least the percentage of sequence identity recited in the claims; and

2) the disclosed species of human CXCR3 (SEQ ID NO: 2) is representative of the genus because all members of the genus have at least 80% or at least 90% amino acid sequence identity to SEQ ID NO:2, and assays suitable for identifying CXCR3 proteins or variants that have the specified binding activity are disclosed.

Therefore, like in Example 14 of the training materials, the instant specification provides adequate written description for claims that recite percent amino acid sequence identity.

Example 9 on page 35 of the training materials relates to written description of claims drawn to nucleic acids that are defined as encoding a protein which binds a receptor and stimulates its activity and hybridizing to a reference nucleic acid. Applying the analysis from

Example 9 of the training materials to the claims of the subject application that recite hybridization conditions reveals:

1) the person of skill in the art would not expect substantial variation among species encompassed by the claimed genus because the high stringency wash conditions recited in the claim yield structurally similar DNAs; and

2) high stringency wash conditions in combination with the coding function of DNA and the level of skill in the art are adequate to allow the person skilled in the art to determine that Applicant was in possession of the claimed invention.

Therefore, like in Example 9 of the training materials, the instant specification provides adequate written description for claims that recite hybridization conditions.

The analysis for claims that recite that the CXCR3 protein or variant is encoded by a nucleic acid sharing at least about 75% or at least about 90% nucleotide sequence similarity with the coding region of SEQ ID NO:1 is essentially the same as for claims that recite hybridization conditions. Therefore, the person of skill in the art would not expect substantial variation among species encompassed by the claimed genus because the percent sequence similarity conditions recited in the claim yield structurally similar DNAs. Therefore, the instant specification provides adequate written description for these claims.

Reconsideration and withdrawal of the rejection in view of the foregoing are respectfully requested.

Rejection of Claims 30-52 and 60-74 Under 35 U.S.C. § 112, First Paragraph

Claims 30-52 and 60-74 are rejected under 35 U.S.C. § 112, first paragraph, because in the Examiner's opinion, "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims." Office Action, at page 8, lines 1-3. The Examiner further states that the claims are overly broad in the recitation of at least about 80% or at least about 90% amino acid sequence identity because "no guidance is provided as to which of the myriad of polypeptide species encompassed by the claim will retain the characteristics of a CXCR3 protein." Id. at lines 4-6. The Examiner cites Mikayama *et al.* and Voet *et al.* as

demonstrating that single amino acid changes or differences in the amino acid sequence of a protein can effect the function of the protein.

It is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id.

The person of ordinary skill in the art would be able to practice the claimed invention following the guidance of the specification and using no more than routine experimentation. Methods suitable for preparing ligand binding variants and functional variants of proteins that contain amino acid additions, deletions and/or substitutions were well known in the art at the time the application was filed. The specification discloses and exemplifies methods for identifying CXCR3 proteins, ligand binding variants that bind IP-10 and/or MIG and functional variants that bind IP-10 and/or MIG and induce a cellular response. Specification at page 39, line 1 *et seq.* and page 70, line 26 *et seq.*, for example. The specification also teaches that CXCR3 is a G protein-coupled receptor and discloses the predicted domain structure of the protein. Id. at page 2, line 22 *et seq.*; page 8, line 22 *et seq.*; and Figure 2. This disclosure together with the knowledge in the art of the structure-function relationship of G protein-coupled receptors, the person of ordinary skill in the art could practice the claimed inventions. In view of the teachings of the specification and knowledge in the art, the person of skill in the art could readily prepare CXCR3 proteins or variants, for example, those sharing at least about 80% or at least about 90% amino acid sequence identity with SEQ ID NO:2, using conventional techniques and screen the proteins for IP-10 and/or MIG binding and/or the capacity to induce a cellular response upon ligand or promoter binding using an assay disclosed in the specification or other suitable assay. Screening proteins, such as receptor proteins, to ascertain binding, signaling and/or cellular response function is considered routine in the art of receptor biology, and does not constitute

undue experimentation. This routine screening is analogous to the screening of hybridomas to identify those hybridomas that produce a desired antibody which the Wands court determined was not undue experimentation. Id.

Evidence that the preparation of variant proteins containing amino acid substitutions and the screen of such variants for binding function are routine in the art is provided by Cunningham and Wells (Reference AW2, of record). Cunningham and Wells describe a study in which 62 muteins of human growth hormone containing single amino acid replacements were prepared and tested for binding to the human growth hormone receptor. Cunningham and Wells teach:

> Single alanine mutations (62 in total) were introduced at every residue contained within the three discontinuous segments of hGH (residue 2 to 19, 54 to 74, and 167 to 191) that have been implicated in receptor recognition.

Cunningham and Wells, Abstract, second sentence.

Thus, Cunningham and Wells specifically selected positions "that have been implicated in receptor recognition" for mutation. Notwithstanding the targeting of the amino acid substitutions to positions implicated in receptor binding, Cunningham and Wells report that "[t]he overall folding of these mutant proteins was indistinguishable from that of the wild-type hGH ...." Id. The results of the study demonstrated that although some mutants had lower affinity for receptor, many of the mutants displayed only minor changes in dissociation constant relative to wildtype (0.34 nM) and some bound with greater affinity. Cunningham and Wells at Table 1 (see, P2A (0.31 nM), T3A (0.31 nM), L9A (0.32 nM), R19A (0.37 nM), etc.). Thus, Cunningham and wells demonstrates that the person of ordinary skill in the art is well equipped to quickly prepare a large variety of mutants without severe impact on tertiary structure, and to assess the mutants for a desired function.

Reconsideration and withdrawal of the rejection are requested.

Information Disclosure Statement

An Information Disclosure Statement (IDS) was filed on August 7, 2000. Acknowledgment of consideration of the information provided therein is requested in the next Office Communication.

Drawing Correction and Formal Drawings

A Transmittal of Proposed Drawing Corrections and New Formal Drawings, with Formal Drawings (sheets 1/4-4/4) was filed on September 25, 2000. Acknowledgment of approval of the proposed corrections in respectfully requested in the next Office Communication.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the title at page 1, lines 5 and 6 with the below title marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

[IP-10/MIG RECEPTOR DESIGNATED CXCR3, NUCLEIC ACIDS, AND] METHODS [OF USE THEREFOR] FOR IDENTIFYING LIGANDS, INHIBITORS OR PROMOTERS OF CXC CHEMOKINE RECEPTOR 3

Replace the title at page 87, lines 1 and 2 with the below title marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

[IP-10/MIG RECEPTOR DESIGNATED CXCR3, NUCLEIC ACIDS, AND] METHODS [OF USE THEREFOR] FOR IDENTIFYING LIGANDS, INHIBITORS OR PROMOTERS OF CXC CHEMOKINE RECEPTOR 3

Replace the paragraph at page 87, lines 15 through 33 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

[Another aspect of t]The invention relates to [isolated and/or recombinant nucleic acids encoding a mammalian (e.g., human) CXCR3 protein and variants thereof, including antisense nucleic acid, recombinant nucleic acid constructs, such as plasmids or retroviral vectors, comprising a nucleic acid which encodes a protein of the present invention or variant thereof, and to host cells comprising a nucleic acid or construct, useful in the production of recombinant proteins. Also encompassed are] methods of identifying ligands, and inhibitors (e.g., antagonists) or promoters (e.g., agonists) of receptor function, including methods in which host cells comprising a nucleic acid encoding a CXCR3 or variant thereof are used in an assay to identify and assess the efficacy of

ligands, inhibitors or promoters. Inhibitors and promoters of receptor function can be used to modulate receptor activity, permitting selective inhibition of lymphocyte function, particularly of effector cells such as activated T lymphocytes and NK cells for therapeutic purposes.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Claims 30, 34, 37, 38, 40-42, 44, 46, 48, 60-75, 81 and 85-92 have been amended and are presented below in amended form and Claims 93-105 are new.

30. (Twice Amended) A method of detecting or identifying an agent which binds a mammalian CXC Chemokine Receptor 3 (CXCR3) protein or ligand binding variant thereof, comprising combining an agent to be tested with a composition comprising an isolated and/or recombinant mammalian CXCR3 protein or ligand binding variant thereof under conditions suitable for binding of ligand [thereto] to said mammalian CXCR3 protein or variant, and detecting or measuring the formation of a complex between said agent and said mammalian CXCR3 protein or variant,

wherein said mammalian CXCR3 protein or ligand binding variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and [wherein said variant] shares at least about 80% amino acid sequence identity with SEQ ID NO:2.

34. (Twice Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or a ligand binding variant thereof comprising:

a) combining an agent to be tested with a host cell expressing recombinant mammalian CXCR3 protein or a ligand binding variant thereof under conditions suitable for binding of ligand [thereto] to said mammalian CXCR3 protein or variant; and

b) detecting or measuring the formation of a complex between said agent and [the] said mammalian CXCR3 protein or [a] ligand binding variant,

wherein said mammalian CXCR3 protein or ligand binding variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and

[wherein said variant] shares at least about 80% amino acid sequence identity with SEQ ID NO:2.

37. (Amended) The method of Claim 34, wherein the mammalian CXCR3 protein or a ligand binding variant thereof can mediate cellular signalling and/or a cellular response, and the formation of a complex is monitored by detecting or measuring a signalling activity or cellular response of said mammalian CXCR3 protein or variant in response thereto.

38. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof comprising:

a) combining an agent to be tested with a ligand of said mammalian CXCR3 protein and a composition comprising isolated and/or recombinant mammalian CXCR3 protein or ligand binding variant thereof under conditions suitable for binding of ligand [thereto] to said mammalian CXCR3 protein or variant; and

b) detecting or measuring the formation of a complex between said mammalian CXCR3 protein or variant and said ligand, whereby inhibition of complex formation by the agent is indicative that the agent is an inhibitor,

wherein said mammalian CXCR3 protein or ligand binding variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and [wherein said variant] shares at least about 80% amino acid sequence identity with SEQ ID NO:2.

40. (Twice Amended) The method of Claim 38, wherein the composition comprising isolated and/or recombinant mammalian CXCR3 protein or ligand binding variant thereof contains a host cell expressing said recombinant mammalian CXCR3 protein or [a] ligand binding variant thereof.

41. (Twice Amended) The method of Claim 40, wherein [the] said mammalian CXCR3 protein or ligand binding variant thereof can mediate cellular signalling and/or a cellular response,

and the formation of a complex is monitored by detecting or measuring a signalling activity or cellular response of said mammalian CXCR3 protein or variant in response thereto.

42. (Twice Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or ligand binding variant thereof comprising:

a) combining an agent to be tested with a ligand of said mammalian CXCR3 protein and a host cell expressing a recombinant mammalian CXCR3 protein or ligand binding variant thereof under conditions suitable for binding of ligand [thereto] to said mammalian CXCR3 protein or ligand binding variant; and

b) detecting or measuring the formation of a complex between said mammalian CXCR3 protein or variant and said ligand, whereby inhibition of complex formation by the agent is indicative that the agent is an inhibitor,

wherein said mammalian CXCR3 protein or ligand binding variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and [wherein said variant] shares at least about 80% amino acid sequence identity with SEQ ID NO:2.

44. (Twice Amended) The method of Claim 42, wherein [the] said mammalian CXCR3 protein or ligand binding variant thereof can mediate cellular signalling and/or a cellular response, and the formation of a complex is monitored by detecting or measuring a signalling activity or cellular response of said mammalian CXCR3 protein or variant in response thereto.

46. (Twice Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested with

(a) a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof, and

(b) a ligand or promoter [thereof] of said mammalian CXCR3 protein or variant, under conditions suitable for detecting a ligand- or promoter-induced response, and assessing the ability of the test agent to inhibit said response, whereby inhibition of a ligand- or promoter-induced response by the agent is indicative that the agent is an inhibitor,

wherein said mammalian CXCR3 protein or functional variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and [wherein said variant] shares at least about 80% amino acid sequence identity with SEQ ID NO:2.

48. (Twice Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein [of] or functional variant thereof comprising combining an agent to be tested with a host cell expressing a recombinant mammalianCXCR3 protein or functional variant thereof under conditions suitable for detecting a receptor-mediated response, and detecting or measuring said response, whereby induction or stimulation of said response by the agent is indicative that the agent is a promoter,

wherein said mammalian CXCR3 protein or functional variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10 and Mig, and [wherein said variant] shares at least about 80% amino acid sequence identity with SEQ ID NO:2.

60. (Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof of Claim 38, wherein said mammalian CXCR3 protein or variant shares at least about 90% amino acid sequence identity with SEQ ID NO:2.

61. (Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof comprising:

a) combining an agent to be tested with a ligand of said mammalian CXCR3 protein and a composition comprising isolated and/or recombinant mammalian CXCR3 protein or a ligand binding variant thereof under conditions suitable for binding of ligand [thereto] to said mammalian CXCR3 protein or variant; and

b) detecting or measuring the formation of a complex between said mammalian CXCR3 protein or variant and said ligand, whereby inhibition of complex formation by the agent is indicative that the agent is an inhibitor,

wherein said mammalian CXCR3 protein or ligand binding variant can selectively bind at least one chemokine selected from the group consisting of IP-10, Mig, a homolog of

IP-10, and a homolog of Mig, and [wherein said variant] is encoded by a nucleic acid sharing at least about 75% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

62. (Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof of Claim 61, wherein said mammalian CXCR3 protein or variant is encoded by a nucleic acid sharing at least about 90% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

63. (Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof of Claim 46, wherein said mammalian CXCR3 protein or variant shares at least about 90% amino acid sequence identity with SEQ ID NO:2.

64. (Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested with

(a) a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof, and

(b) a ligand or promoter thereof, under conditions suitable for detecting a ligand- or promoter-induced response, and assessing the ability of the test agent to inhibit said response, whereby inhibition of a ligand- or promoter-induced response by the agent is indicative that the agent is an inhibitor,

wherein said mammalian CXCR3 protein or functional variant can selectively bind at least one chemokine selected from the group consisting of IP-10, Mig, a homolog of IP-10, and a homolog of Mig, and [wherein said variant] is encoded by a nucleic acid sharing at least about 75% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

65. (Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof of Claim 64, wherein said mammalian CXCR3 protein

or variant is encoded by a nucleic acid sharing at least about 90% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

66. (Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein or functional variant thereof of Claim 48, wherein said mammalian CXCR3 protein or variant shares at least about 90% amino acid sequence identity with SEQ ID NO:2.

67. (Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested with a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof under conditions suitable for detecting a receptor-mediated response, and detecting or measuring said response, whereby induction or stimulation of said response by the agent is indicative that the agent is a promoter, wherein said mammalian CXCR3 protein or functional variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10, Mig, a homolog of IP-10, and a homolog of Mig, and [wherein said variant] is encoded by a nucleic acid sharing at least about 75% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

68. (Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein or functional variant thereof of Claim 67, wherein said mammalian CXCR3 protein or variant is encoded by a nucleic acid sharing at least about 90% nucleotide sequence similarity with the coding region of the sequence illustrated in SEQ ID NO:1.

69. (Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or ligand binding variant thereof of Claim 30, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or ligand binding variant thereof.

70. (Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or a ligand binding variant thereof of Claim 34, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or ligand binding variant thereof.

71. (Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof of Claim 38, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or ligand binding variant thereof.

72. (Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or ligand binding variant thereof of Claim 42, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or ligand binding variant thereof.

73. (Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof of Claim 46, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or functional variant thereof.

74. (Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein of functional variant thereof of Claim 48, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or functional variant thereof.

75. (Amended) A method of detecting or identifying an inhibitor of ligand binding to a human CXCR3 protein comprising:

a) combining an agent to be tested with a ligand of said CXCR3 protein and a composition comprising recombinant human CXCR3 protein under conditions suitable for binding of ligand thereto; and

b) detecting or measuring the formation of a complex between said CXCR3 protein and said ligand, whereby inhibition of complex formation by the agent is indicative that the agent is an inhibitor, wherein said human CXCR3 protein [can] selectively binds [to] at least one chemokine selected from the group consisting of human IP-10 or human Mig and comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2).

81. (Amended) A method of detecting or identifying an inhibitor of ligand binding to a human CXCR3 protein comprising:

a) combining an agent to be tested with a ligand of said human CXCR3 protein and a host cell expressing a recombinant human CXCR3 protein under conditions suitable for binding of ligand [thereto] to said human CXCR3 protein; and

b) detecting or measuring the formation of a complex between said protein and said ligand, whereby inhibition of complex formation by the agent is indicative that the agent is an inhibitor, wherein said human CXCR3 protein [can] selectively binds [to] at least one chemokine selected from the group consisting of human IP-10 or human Mig and comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2).

85. (Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or ligand binding variant thereof, comprising combining an agent to be tested with a composition comprising an isolated and/or recombinant mammalian CXCR3 protein or ligand binding variant thereof under conditions suitable for binding of ligand [thereto] to said mammalian CXCR3 protein or variant, and detecting or measuring the formation of a complex between said agent and said mammalian CXCR3 protein or variant, wherein said mammalian CXCR3 protein or ligand binding variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10, Mig, a homolog of IP-10, and a homolog of Mig, and [wherein said variant] is encoded by a nucleic acid that hybridizes, under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes, to a nucleic acid selected from the group consisting of:

a) the complement of SEQ ID NO:1; and

b) [a nucleic acid complementary to SEQ ID NO:1; and

c)] the complement of a portion of [a) or b)] SEQ ID NO:1 comprising the open reading frame [of SEQ ID NO:1].

86. (Amended) A method of detecting or identifying an agent which binds a mammalian CXCR3 protein or ligand binding variant thereof of Claim 85, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or ligand binding variant thereof.

87. (Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof comprising:

a) combining an agent to be tested with a ligand of said mammalian CXCR3 protein and a composition comprising isolated and/or recombinant mammalian CXCR3 protein or a ligand binding variant thereof under conditions suitable for binding of ligand [thereto] to said mammalian CXCR3 protein or variant; and

b) detecting or measuring the formation of a complex between said mammalian CXCR3 protein or variant and said ligand, whereby inhibition of complex formation by the agent is indicative that the agent is an inhibitor,

wherein said mammalian CXCR3 protein or ligand binding variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10, Mig, a homolog of IP-10, and a homolog of Mig, and [wherein said variant] is encoded by a nucleic acid that hybridizes, under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes, to a nucleic acid selected from the group consisting of:

[a] i) the complement of SEQ ID NO:1; and

[b] ii) [a nucleic acid complementary to SEQ ID NO:1; and

c)] the complement of a portion of [a) or b)] SEQ ID NO:1 comprising the open reading frame [of SEQ ID NO:1].

88. (Amended) A method of detecting or identifying an inhibitor of ligand binding to a mammalian CXCR3 protein or a ligand binding variant thereof of Claim 87, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or ligand binding variant thereof.

89. (Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested with

(a) a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof, and

(b) a ligand or promoter thereof, under conditions suitable for detecting a ligand- or promoter-induced response, and assessing the ability of the test agent to inhibit said response, whereby inhibition of a ligand- or promoter-induced response by the agent is indicative that the agent is an inhibitor,

wherein said mammalian CXCR3 protein or functional variant [can] selectively binds at least one chemokine selected from the group consisting of IP-10, Mig, a homolog of IP-10, and a homolog of Mig, and [wherein said variant] is encoded by a nucleic acid that hybridizes, under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes, to a nucleic acid selected from the group consisting of:

[a] i) the complement of SEQ ID NO:1; and

[b] ii) [a nucleic acid complementary to SEQ ID NO:1; and

c)] the complement of a portion of [a) or b)] SEQ ID NO:1 comprising the open reading frame [of SEQ ID NO:1].

90. (Amended) A method of detecting or identifying an inhibitor of a mammalian CXCR3 protein or functional variant thereof of Claim 89, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or functional variant thereof.

91. (Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein or functional variant thereof comprising combining an agent to be tested with a host cell expressing a recombinant mammalian CXCR3 protein or functional variant thereof under conditions suitable for detecting a receptor-mediated response, and detecting or measuring said response, whereby induction or stimulation of said response by the agent is indicative that the agent is a promoter, wherein said mammalian CXCR3 protein or functional variant

[can] selectively binds at least one chemokine selected from the group consisting of IP-10, Mig, a homolog of IP-10, and a homolog of Mig, and [wherein said variant] is encoded by a nucleic acid that hybridizes, under high stringency wash conditions of 2X SSC, 0.1% SDS at room temperature for ten minutes followed by two washes in 1X SSC, 0.1% SDS at 65°C for thirty minutes and a final wash in 0.5X SSC, 0.1% SDS at 65°C for ten minutes, to a nucleic acid selected from the group consisting of:

[a] i) the complement of SEQ ID NO:1; and

[b] ii) [a nucleic acid complementary to SEQ ID NO:1; and

c)] the complement of a portion of [a) or b)] SEQ ID NO:1 comprising the open reading frame [of SEQ ID NO:1].

92. (Amended) A method of detecting or identifying a promoter of a mammalian CXCR3 protein of functional variant thereof of Claim 91, wherein the mammalian CXCR3 protein or variant thereof is a human CXCR3 or functional variant thereof.